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Remarks

Claims 1-13 are pending in the subject application and are now presented to the Examiner for further review. Favorable consideration of these claims, in view of the remarks set forth herein, is earnestly solicited.

Claims 1-4 and 6-18 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Ninomiya *et al.* (U.S. Patent No. 4,695,568) in view of Davies *et al.* (U.S. Patent No. 6,008,227). As an initial matter, the applicants wish to point out that only claims 1-13 are pending in the subject application. From a review of the Examiner's grounds for setting forth this obviousness rejection, it appears that the Examiner intended for this rejection to apply to claims 1-13. In any event, the applicants respectfully traverse this ground for rejection because the cited references, taken either alone or in combination, do not disclose or suggest the applicants' unique and advantageous use of 4-2(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof to treat pain, functional bowel disorder, or fibromyalgia.

The Ninomiya reference teaches that 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine monohydrate hydrochloride (MCI-225) is potentially useful for the treatment of depression. However, the only evidence provided by Ninomiya to support this proposition is that the compound "has an antagonistic activity against the hypothermal activity of reserpine". Ninomiya does not discuss the mechanism by which the compound produces such an effect, nor can any mechanism be deduced from the results presented.

The effects of drugs on reserpine-induced hypothermia in animals have been studied for many years and various classes of drugs, some associated with anti-depressant activity and some not, have found to be active in the test.

Examples are given below.

In 1962 Griesemer et al (Proc. West. Pharmacol. Soc., 5, 7-8) showed that dopa antagonised reserpine hypothermia in mice. L-Dopa is currently used in the treatment of Parkinson's disease.

In 1975, Sofia et al (Arch. Int. Pharmacodyn. Ther. 214, 68-74) showed that ketamine reversed reserpine hypothermia in mice. Ketamine is currently used in the clinic as an anaesthetic. It is not used as an anti-depressant.

In 1980, Ross (Acta. Pharmacol. Toxicol. (Copenh.) 47, 347-350) reported that several beta adrenoceptor agonists including terbutaline, salbutamol, and clenbuterol all reversed reserpine induced hypothermia in mice. Salbutamol, for example, is used in the treatment of asthma. To the applicants' knowledge, beta adrenoceptor agonists are not used as anti-depressants.

In 1981, Rogoz et al (Pol. J. Pharmacol. Pharm. 33, 321-335) showed that 5 classical antihistamines, chlorpheniramine, diphenhydramine, chlorcyclizine, chlorpyramine and thenalidine, all antagonised reserpine induced hypothermia. These types of antihistamine are used in the treatment of allergic rhinitis and are not anti-depressants.

In 1983, Przegalinski et al (Pol. J. Pharmacol. Pharm. 35, 233-240) showed that 3 phosphodiesterase inhibitors IBMX, rolipram and Ro-201724 all inhibited reserpine induced hypothermia in mice. Phosphodiesterase inhibitors of this type have been considered for the treatment of asthma and chronic obstructive pulmonary disease.

In 1983, Wachtel (Neuropharmacology 22, 267-272) also showed that selective cAMP phosphodiesterase inhibitors (PDE 4 inhibitors), rolipram, ICI 63 197 and Ro-20-1724 inhibited reserpine induced hypothermia in mice and that all 3 were more potent than imipramine in this effect. Despite being known of for many years, PDE 4 inhibitors are not used clinically as anti-depressants.

In 1987, Frances et al (Pharmacol, Biochem, Behav, 27, 21-24) reported that reserpine induced hypothermia in mice is completely inhibited by dobutamine, which they describe as a beta adrenoceptor agonist specific for beta 1 receptors. Dobutamine is currently used in the treatment of congestive heart failure but not as an anti-depressant.

In 1993, Moryl et al (Pharmacol. Toxicol. 72, 394-397) reported that amantadine and its dimethyl derivative memantine, were active against reserpine induced hypothermia in animals. Amantadine is used clinically as an antiviral agent, but not as an anti-depressant. Memantine, which is a selective N-methyl-D-aspartate (NMDA) receptor antagonist has recently been tested clinically in major depression and found not to be effective (Zarate et. al. 2006, Am. J. Psychiatry 163, 153-155).

In 1996, Miyamoto et al (J. Pharmacol. Exp. Ther. 277, 1292-1304) reported that TAK-147, a novel acetylcholinesterase inhibitor, reversed reserpine induced hypothermia in mice. To the applicants' knowledge acetylcholinesterase inhibitors have not been considered as anti-depressants.

In 1998, Bruhwyler et al (Behav. Pharmacol.) reported that pirlindole, a reversible and selective monoamine oxidase type A inhibitor, was active against reserpine hypothermia.

Thus, it is clear that many of the compounds that are active in the reserpine hypothermia model are not anti-depressants. Accordingly, the Ninomiya reference provides no basis for concluding that 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine monohydrate hydrochloride (MCI-225) is an effective anti-depressant. Certainly, Ninomiya do not provide any disclosure whatsoever as to any mode of anti-depressant action of MCI-225 even if one was to assume that it has anti-depressant action at all.

A further assumption upon which the obviousness rejection is based is also very tenuous. Specifically, the Office Action suggests that all anti-depressants are drugs that inhibit monoamine uptake mechanisms, through the dopamine, 5HT and norepinephrine transporters. This line of reasoning ignores other major classes of anti-depressants, for example MAO inhibitors, which act by a completely different mechanism to monoamine uptake.

Thus, the obviousness rejection is based, in part, on two assumptions, neither of which is well-founded. One assumption is that all compounds that are active against reserpine-induced hypothermia in animals are anti-depressants. This is untrue as evidence by the numerous literature citations provided above. The second faulty assumption is that all anti-depressants inhibit monoamine uptake mechanisms.

A finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. Here, neither reference contains a suggestion to utilize MCI-225 in the treatment of pain, functional bowel disorder, or fibromyalgia. It is only the applicants' disclosure that provides such a teaching, and the applicants' disclosure cannot be used to reconstruct the prior art for a rejection under §103. This was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

> The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading

> into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 112 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

The mere fact that the purported prior art could have been modified or applied in a manner to yield the applicants' invention would not have made the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). As the CAFC has established, an invention will not be rendered obvious merely by combining teachings found in the prior art. *ACS Hospital Systems, Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984). There must be some suggestion or incentive in the prior art to make the combination. *Id.* Also, the prior art must suggest that this combination would have a reasonable likelihood of success. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

There is no reason for the person skilled in the art to consider the two cited references in combination. Nor does the Office Action take into account the complex pharmacology of MCI-225. In view of this unpredictability in the art, the subject invention cannot be fairly stated to be obvious. At most, it may have been obvious to try this unique method. The "obvious to try" standard has long been held to be an inappropriate basis for a §103 rejection. See, for example, *In re Antonie*, 195 USPQ 6 (CCPA 1977); *In re Dow Chemical Co.*, 5 USPQ 2d 1529 (CAFC 1988). Therefore, the results of applicants' empirical research are not rendered obvious by the cited references. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §103 based on Ninomiya in view of Davies *et al.*

Claims 5-11 have been provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 1-7 of copending Application No. 10/519,594. Upon an indication of allowability of the claims in the current case, the applicants will either cancel or amend the claims in the '594 application.

Claims 12 and 13 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 30, 31 and 35 of copending Application No. 10/525,532. Upon an indication of the allowability of claims 12 and 13 in the current application, the applicants will entertain filing a Terminal Disclaimer with respect to the '532 application.

Docket No. GJE-6757C1
Serial No. 10/617,847

In view of the foregoing remarks and the amendment above, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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